

CLINICAL VIGNETTE

The Gastric Ulcer that Wouldn't Heal

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Case Summary

A 31-year-old female presented with abdominal pain which began while on a trip to Cancun. During her trip, she developed abdominal pain, nausea, vomiting, and mild constipation. She denied fever or diarrhea. Upon her return, she continued to have pain as well as weight loss, and presented to her primary doctor for further evaluation. Basic labs were normal. She also saw her gynecologist as she has a history of chronic pain due to endometriosis. She was given a prescription for Ketorolac and Oxycodone for presumed endometriosis pain. She continued to have pain, nausea and weight loss and presented to the emergency room. Abdominal US and CT scan of the abdomen and pelvis were normal. She was discharged home with pain medications and ondansetron. She continued to feel poorly and returned to her PCP, where repeat labs were remarkable for hemoglobin of 9.9 g/dl, MCV of 86 fl, and Platelets of $431 \times 10^3/\mu\text{l}$, and ESR of 82 mm/hr. Comprehensive metabolic panel was unremarkable and she was started on empiric Ciprofloxacin and Metronidazole and referred to Gastroenterology.

Gastroenterology consultation was obtained approximately 2 months after her pain began in Cancun. She reported ongoing epigastric and right upper quadrant pain, colicky in nature, occurring for 1 hour at a time, and at times waking her up from sleep. She reported no further nausea or vomiting, but did note a 15-lb unintentional weight loss over the past 2 months. Notably, the pain was different than her usual endometriosis pain. The remainder of her medical history was unremarkable except for ibuprofen 800 mg taken regularly for endometriosis pain, and excedrin as needed for headaches.

On physical exam, vital signs were normal, weight was 123lbs with a BMI of 18. She had tenderness to minimal palpation in the epigastric region, right upper quadrant and left upper quadrant. The remainder of her exam was normal.

Upper endoscopy shortly after consultation revealed a giant, clean based, antral ulcer along the greater curvature of the stomach. (Figures 1 and 2). Biopsies revealed chronic gastritis with reactive stromal change consistent with ulcer edge, no evidence of malignancy or H. Pylori. She was placed on proton pump inhibitor (PPI) twice daily, Carafate suspension four times daily, and advised to avoid all NSAIDs.

At follow-up 2 weeks later she was feeling much better, with return of appetite, increased energy, and a weight gain of about 5lbs. Her abdominal pain had significantly improved.

Ten weeks later, she underwent a second upper endoscopy to ensure ulcer healing. The previously seen giant ulcer was now smaller but still present. Several new, deep antral ulcers were also noted. (Figures 3-5). Biopsies again revealed chronic gastritis with focal ulceration, and focally increased eosinophils, consistent with reaction to ulceration.

At scheduled office visit two weeks later, she denied any NSAID use, tobacco, alcohol or other substance abuse and was compliant with PPI twice daily. Repeat testing for H. Pylori was negative (including stool antigen and serum antibody), and serum gastrin and calcium levels were normal. Ranitidine 300mg twice daily was added to her PPI regimen, and she was referred for a repeat endoscopy with endoscopic ultrasound.

Her third upper endoscopy included normal EUS. The endoscopy revealed four small antral ulcers, which were improved from the prior exam. (Figures 6-7). Biopsies again showed chronic gastritis, without H. Pylori or features consistent with eosinophilic gastroenteritis. Her symptoms were improved, therefore the plan was to continue her current regimen, and repeat the endoscopy after 2-3 months to ensure ongoing ulcer healing.

Four weeks later, she presented to the urgent care with recurrent abdominal pain and blood tinged emesis. Her hemoglobin was 12.8 g/dl. She reported 2 weeks of worsened abdominal pain along with loss of appetite. A fourth upper endoscopy revealed a large, 5cm antral ulcer, similar in appearance to the original giant ulcer seen on her first endoscopy 6 months prior. (Figures 8 and 9). Gastric mapping was performed and again biopsies returned as chronic gastritis without new pathology.

Due to the refractory nature of her ulcer, failure of medical management, and her ongoing symptoms of abdominal pain and weight loss, she was referred to surgery. She underwent a laparoscopic distal antrectomy, truncal vagotomy, hiatal hernia repair, gastrojejunostomy (Billroth II reconstruction), and extensive lysis of adhesions.

Her operative findings were notable for a large 6 cm gastric ulcer with posterior perforation into the pancreas. The ulcer penetrated entirely through the posterior wall of the stomach through to the pancreas, with no residual gastric wall at the point of perforation. The ulcer was contained within the lesser sac, explaining the non-resolution of symptoms and non-healing of the ulcer. Final pathology again confirmed marked chronic gastritis with a perforated ulcer.

Four weeks after surgery she was doing quite well. The abdominal pain and nausea had resolved, appetite had returned, and she had regained much of the weight she previously lost.

Discussion

NSAIDs are one of the most common causes of peptic ulcer disease, primarily by blocking the cyclooxygenase enzymes responsible for producing prostaglandins (PG). Prostaglandins protect the gastroduodenal mucosa by reducing gastric acid secretion, stimulation of mucin and bicarbonate by epithelial cells, enhancing mucosal blood flow and oxygen delivery, and increasing epithelial cell migration toward the luminal surface. Gastric and duodenal injury by acid and pepsin can occur when these protective functions are compromised as a consequence of PG deficiency induced by NSAIDs. This damage may eventually lead to gastric and/or duodenal ulcer formation. Aspirin doses as low as 10mg/day inhibit gastric PG generation and can damage the stomach.¹

Guidelines on chronic NSAID use identify several risk factors associated with increased complications including bleeding, obstruction and perforation. These risk factors include age >65, a history of an uncomplicated ulcer, high dose NSAID therapy, concurrent use of aspirin, steroids, anticoagulants, and possibly SSRI. Recommendations to reduce risk with chronic NSAID use include testing and treating H. Pylori, minimize dose and duration of treatment, and concomitant PPI in those at moderate or high risk for GI toxicity.^{2,3}

Giant gastric ulcers are much less common today, due to the widespread use of anti-secretory therapy. Gastric ulcers greater than 3cm tend to occur in older patients, often present with atypical symptoms such as anorexia and weight loss, and have a higher incidence of bleeding, complications and need for surgery.

After identification of a gastric ulcer, surveillance endoscopy is typically performed after 8 to 10 weeks to ensure ulcer healing. The rationale behind surveillance endoscopy is to rule out malignancy, which can occur even with initial benign appearance. Surveillance endoscopy has lower yield with duodenal ulcers (DU), as 90% heal with H. Pylori eradication (if present), acid suppression and discontinuation of NSAIDs. Given the low risk of malignancy in patients with DU, repeat upper endoscopy is not recommended routinely unless symptoms persist. The ASGE guidelines recommend surveillance endoscopy for the following clinical scenarios:⁴

- Gastric ulcer with appearance suspicious for malignancy, even if biopsy samples from index endoscopy are benign
- Ongoing symptoms despite treatment

- Gastric ulcer without a clear etiology
- No biopsy or inadequate on index endoscopy
- Index endoscopy done during episode of GI bleeding
- Giant ulcer
- Greater risk factors for gastric cancer: age >50, H. Pylori, immigrants from a region with high prevalence of gastric cancer, family history of gastric CA

Surveillance endoscopy is actually not necessary if the patient is at low risk for gastric cancer and the ulcer appears benign, with a clear cause such as NSAID use and initial negative biopsies, especially if asymptomatic. In these patients, surveillance endoscopy has been low yield.

A refractory peptic ulcer is defined as an endoscopically proven ulcer >5mm that does not heal after 12 weeks of PPI therapy. A recurrent ulcer is one which develops following complete ulcer healing. Approximately 5-10% of ulcers are refractory to PPI therapy. About 5-30% of ulcers recur within the first year if H. Pylori is not successfully eradicated.⁵

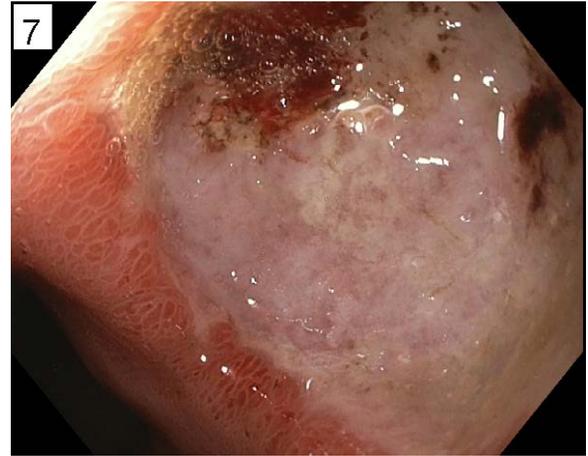
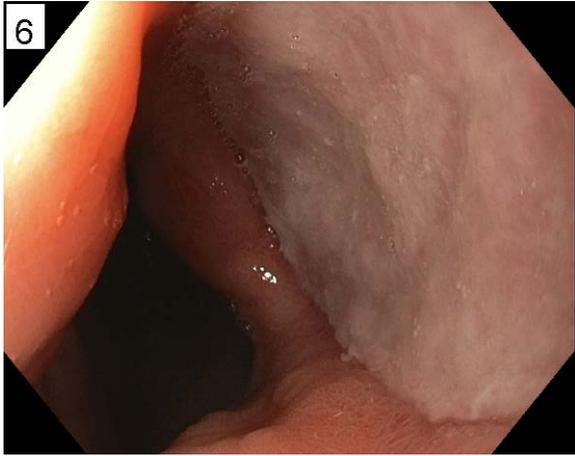
There are several causes of refractory peptic ulcer disease, and a thorough investigation should be performed in patients with persistent gastric ulcers, despite 12 weeks of PPI therapy. Biopsies of non-healing ulcers are needed to exclude underlying malignancy, even if index biopsies were normal. Compliance with PPI therapy needs confirmation. Persistent H. Pylori infection is also a common cause, often because of false negative testing, non-compliance with therapy, or failure to check for eradication after treatment. Approximately 40% of cases of refractory PUD are due to ongoing NSAID use. Other substances such as tobacco, cocaine, methamphetamines can impair ulcer healing. Co-morbid diseases such as respiratory failure, renal failure, cirrhosis, uremia, critical illness are all associated with poor ulcer healing. Ulcer characteristics such as large size, presence of dense scarring, or low mucosal blood flow or ischemic state can adversely affect ulcer healing. Hypersecretory states such as Zollinger-Ellison syndrome ZE and hyperparathyroidism should be ruled out by checking serum gastrin and calcium levels. Rare and unusual causes of refractory PUD include sarcoidosis, lymphoma, Crohn's disease, ischemia, and eosinophilic gastroenteritis.

Surgical management remains the mainstay of treatment for ulcer related complications and severe refractory disease. The goals of surgery are to treat or prevent ulcer complications, reduce acid secretion to permit ulcer healing and prevent recurrence, and minimize post-operative complications.

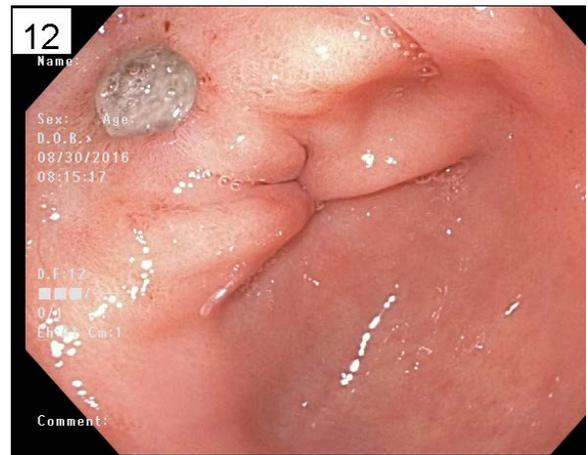
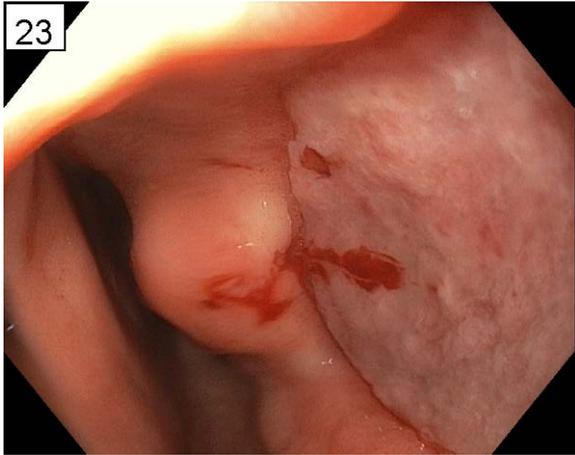
Conclusion

Giant gastric ulcers >3cm are infrequently encountered but carry a higher risk of complications and potential need for surgery. Refractory PUD should prompt an evaluation for ongoing NSAID use, untreated H. Pylori, concurrent smoking or substance abuse, or other more rare conditions such as Crohn's disease, sarcoidosis and ZE. Imaging should be considered in cases of refractory PUD and a surgical consultation should be obtained in those who fail medical management.

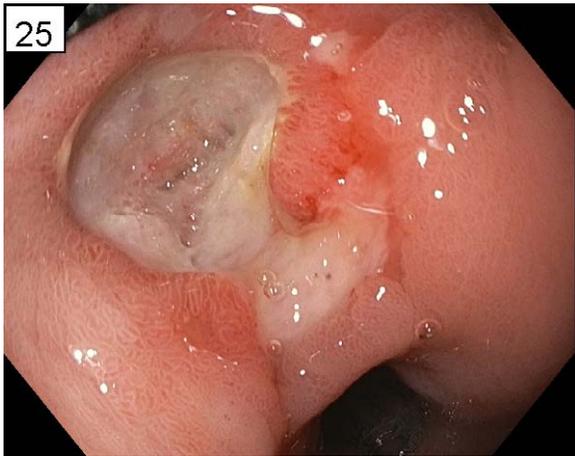
Figures 1 and 2: EGD #1, giant gastric ulcer in the antrum.



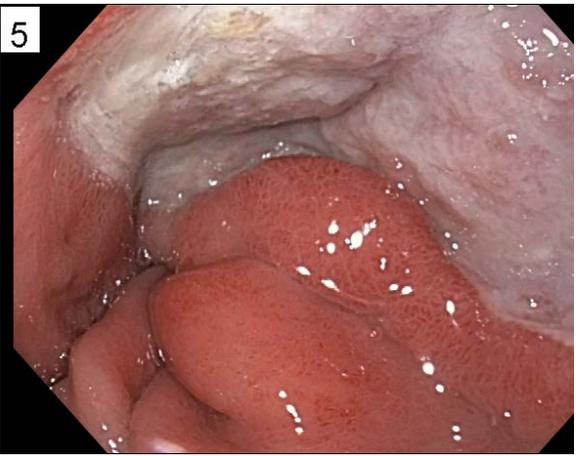
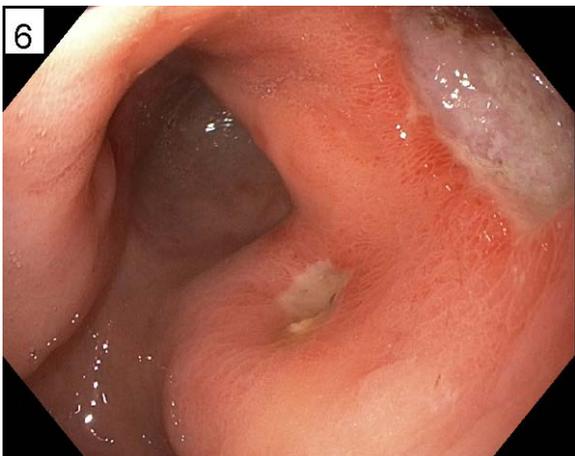
Figures 6 and 7: EGD #3, smaller antral ulcers.

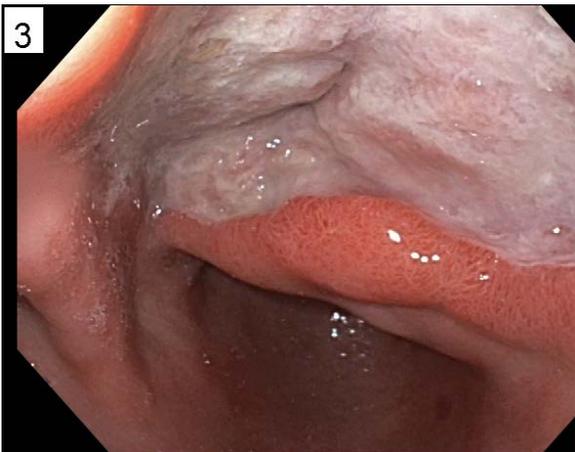


Figures 3-5: EGD #2, giant antral ulcer is smaller, but additional new deep antral ulcers present.



Figures 8 and 9: EGD#4, recurrent giant antral ulcer.





REFERENCES

1. **Kelly JP, Kaufman DW, Jurgelon JM, Sheehan J, Koff RS, Shapiro S.** Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. *Lancet.* 1996 Nov 23;348(9039):1413-6. PubMed PMID: 8937281.
2. **Lanza FL, Chan FK, Quigley EM;** Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol.* 2009 Mar;104(3):728-38. doi:10.1038/ajg.2009.115. Epub 2009 Feb 24. PubMed PMID: 19240698.
3. **Dall M, Schaffalitzky de Muckadell OB, Lassen AT, Hansen JM, Hallas J.** An association between selective serotonin reuptake inhibitor use and serious upper gastrointestinal bleeding. *Clin Gastroenterol Hepatol.* 2009 Dec;7(12):1314-21. doi: 10.1016/j.cgh.2009.08.019. Epub 2009 Aug 26. PubMed PMID: 19716436.
4. **Leodolter A, Kulig M, Brasch H, Meyer-Sabellek W, Willich SN, Malfertheiner P.** A meta-analysis comparing eradication, healing and relapse rates in patients with Helicobacter pylori-associated gastric or duodenal ulcer. *Aliment Pharmacol Ther.* 2001 Dec;15(12):1949-58. PubMed PMID: 11736726.
5. **Ford AC, Delaney BC, Forman D, Moayyedi P.** Eradication therapy in Helicobacter pylori positive peptic ulcer disease: systematic review and economic analysis. *Am J Gastroenterol.* 2004 Sep;99(9):1833-55. Review. PubMed PMID: 15330927.